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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,001	11/03/2005	Tetsu Akiyama	3190-078	7470

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KILYK & BOWERSOX, P.L.L.C.
400 HOLIDAY COURT
SUITE 102
WARRENTON, VA 20186

EXAMINER	
SHIN, DANA H	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,001	AKIYAMA ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007 and 05 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-42 and 44-51* is/are pending in the application.

4a) Of the above claim(s) *27-32,35,36,39-41 and 44-51* is/are withdrawn from consideration.

5)☒ Claim(s) *37* is/are allowed.

6)☒ Claim(s) *26,33,34,38 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on January 24, 2007, February 5, 2007, and February 8, 2007.

Currently, claims 26-42 and 44-51 are pending. Claims 27-32, 35-36, 39-41, and 44-51 as well as SEQ ID NOs: 2-4 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. See applicant's original election of an invention in the reply filed on July 14, 2006.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 102

Claims 26, 33, and 34 remain rejected under 35 U.S.C. 102(a) as being anticipated by Jimbo et al. (*Molecular Medicine,* 2002) for the reasons of record as set forth in the Office action mailed on August 24, 2006 and for the reasons stated below.

Applicant's arguments filed on January 24, 2007 and February 5, 2007 have been fully considered but they are not persuasive. Applicant contends that the reference of Jimbo et al. is the work of the present inventors and is not by another. The declaration under 37 CFR 1.132 filed on February 8, 2007 is insufficient to overcome the rejection of claims 26, 33, and 34 based upon Jimbo et al. as set forth in the last Office action because the third named inventor of the instant application, Rina Satoh (or Rina Esashi)[1], was not an author of the Jimbo et al. reference, while applicant acknowledges that the actual inventors of claims 26, 33, and 34 are **three people including Rina Satoh (or Rina Esashi)**. See pages 6-7 of the remarks filed on February 5, 2007, which states, "the actual inventors of the present invention are Tetsu Akiyama, Yoshihiro Kawasaki, and Rina Satoh." Therefore, even if Takeshi Jimbo was not an inventor as declared by two of the three named inventors for the present application, the issue with Rina Satoh (or Rina Esashi) still remains unresolved and unsubstantiated in the replies filed on January 24, 2007, February 5, 2007, and February 8, 2007. The term "others" in 35 U.S.C. 102(a) refers to any entity which is different from the inventive entity. The entity need only differ by one person to be "by others." This holds true for all types of references eligible as prior art under 35 U.S.C.

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1. The applicant refers to the third named inventor as "Rina Satoh" in the remarks filed on January 24, 2007 and February 5, 2007. It is noted that the Application Data Sheet lists "Rina Satoh" as the third inventor, while the declaration is signed with "Rina Esashi". Clarification is required.

102(a) including publications as well as public knowledge and use. See MPEP §2132. Since the inventive entity of the Jimbo et al. reference is different, even without Takeshi Jimbo, from that of the instantly claimed invention, and since no declaration has been filed to support the discrepancy between the inventive entity of the Jimbo et al. reference and that of the instant application, the Jimbo et al. reference is deemed prior art by "another" to the present application, and thus, claims 26, 33, and 34 stand rejected under 35 U.S.C. 102(a) as being anticipated by Jimbo et al. (*Molecular Medicine,* 2002).

Claim 26 remains rejected under 35 U.S.C. 102(e) as being anticipated by Drmanac et al. (US 2003/0073623 A1) for the reasons of record as set forth in the Office action mailed on August 24, 2006 and for the reasons stated below.

Applicant's arguments filed on January 24, 2007 and February 5, 2007 have been fully considered but they are not persuasive. Applicant argues that there is no specific enabling teachings of the antisense RNA or DNA disclosed in Drmanac et al. Further, applicant argues that the optimal length of a DNA fragment to show an RNA interference effect is about 21 mer. These arguments provided by applicant are immaterial to the instant application because enablement issue is not addressed for product claims unless directed to "pharmaceutical compositions" and because claim 26, as claimed and currently amended, reads not only on RNA interference but also on antisense inhibition. Moreover, SEQ ID NO:1 claimed in the instant application is 31 mer, which, according to applicant, should exhibit non-specific effects. Contrary to applicant's assertions, Drmanac et al. expressly teach that a nucleic acid inhibitor (e.g., antisense) comprising 20 to 40 bases that are complementary to a region of the target gene

can be designed (paragraphs 0012 and 0183). Further, they teach SEQ ID NO:1044 (459 mer), which is the GEF4 mRNA sequence. In response to applicant's argument that the Drmanac et al. reference does not teach the limitation of "for inhibiting metastasis of colorectal cancer", a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Since the instant specification expressly teaches that an inhibitor of GEF activity can be used to inhibit Asef (pages 1-12), if one of ordinary skill in the art were to take 20 to 40 bases of SEQ ID NO:1044 of Drmanac et al. as taught by their disclosure, the fragment of SEQ ID NO:1044 will inhibit expression of Asef by antisense inhibition and thereby inherently inhibit metastasis of colorectal cancer, as claimed in claim 26.

Claim Rejections - 35 USC § 103

Claims 26 and 33-34 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kawasaki et al. (*Science,* 2000, 289:1194-1197, applicant's citation, IDS filed on August 11, 2005) in view of Fire et al. (US 6,506,559 B1) and Costa et al. (US 2003/0157531 A1) for the reasons of record as set forth in the Office action mailed on August 24, 2006 and for the reasons stated below.

Applicant's arguments filed on January 24, 2007 and February 5, 2007 have been fully considered but they are not persuasive. Applicant argues that one of ordinary skill in the art, at the time the instantly claimed invention was made, would not have been able to make a correlation between a molecule relating to cell motility in colorectal cells and its participation in

the metastasis of colorectal cancer. As stated on the previous page, the recitation of the intended use of the claimed invention, namely, "for inhibiting metastasis of colorectal cancer", must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim limitations. Since Kawasaki et al. teach biological implications of Asef gene in colorectal cells in addition to disclosing the Asef gene sequence, and since Fire et al. teach that siRNA molecules can be used to inhibit specific target genes, and since Costa et al. teach that colorectal cancer metastasis can be inhibited by siRNA molecules, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the prior art and make an siRNA agent targeted to the sequence of Asef gene. Further, contrary to applicant's assertions, one of ordinary skill in the art would have been highly motivated to target Asef gene sequence to inhibit colorectal cancer metastasis because Kawasaki et al. expressly teach that the cells transfected with full-length Asef exhibit membrane ruffles and lamellipoida, which are hallmark characteristics recognized as cellular motility and growth in the art. See page 1195. Furthermore, Kawasaki et al. teach that Asef –APC complex may regulate the actin cytoskeletal network, cell morphology, and migration and that APC is responsible for familial colorectal cancer (see Abstract and page 1194). In view of the teachings that link Asef to a gene associated with colorectal cancer and based on the information regarding the role of Asef in actin cytoskeletal network, cell morphology, and migration, any ordinary skill in the art would have been motivated to make an agent that targets the Asef gene, particularly since the genetic sequence of the Asef gene was

taught by Kawasaki et al. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious over the combined teachings of the prior art at the time of filing.

New Rejections Necessitated by Amendments

Claim Objections

Claim 33 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 26. The currently amended claim 26 is identical to claim 33 *verbatim*, except the alternative language of "or by antisense inhibition on the expression of the gene" in lines 3-4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 38 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is necessitated by the amendments entered in claim 38.

The factors to be considered in determining whether undue experimentation is required

are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The claim is drawn to a pharmaceutical composition comprising an oligonucleotide consisting of SEQ ID NO:1 and a pharmaceutical carrier. As such, the claimed composition must be enabled for *in vivo* pharmaceutical therapeutics at the time of filing.

Problems related to therapeutic use of nucleic acids were well known in the art at the time of invention. See for example the reference of Opalinska et al. (*Nature Reviews Drug Discovery*, 2002, 1:503-514), which states on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA."
>
> and in column 2 of the same page,
>
> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately

> targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Although the state of the prior art at the time of filing did enable any skilled person in the art to inhibit gene expression via antisense oligonucleotide in cultured cells without undue experimentation, the teachings of the DNA-based gene therapy art warn against extremely low success of the introduction of DNA-based drugs for human use even after the instant application was filed. See for example, the review article by Patil et al. (*American Association of Pharmaceutical Scientists Journal,* 2005, 7(1):E61-E77) on page E62, which teaches the following:

> "Despite many favorable characteristics and signs of possible clinical victories (see Table 1), the introduction of DNA-based drugs for human use can be best described as limited, with rare successes. The inertia in the development of these drugs can be attributed, in part, to their poor cellular uptake profile *in vivo.* The innate ability of DNA-based drugs to be internalized by target cells is minimal under normal circumstances. In addition, poor biological stability and a short half-life result in unpredictable pharmacokinetics....The resulting random delivery profile of DNA-based drugs is further complicated by a lack of *in vivo/in vitro* correlation of their pharmacological outcomes."

In view of the foregoing, the specification must provide working examples and specific guidance to overcome the art-recognized unpredictability of DNA-based gene therapeutic compositions. Nevertheless, the instant specification is completely silent about any *in vivo* therapeutic effect mediated by an oligonucleotide consisting of SEQ ID NO:1. The specification, however, provides *in vivo* examples wherein the occurrence of colorectal tumor in mice is reduced after administering dominant-negative APC constructs named "Asef-ABR".

In light of the above, it would have been unpredictable whether the claimed invention would have elicited successful inhibition of Asef function/expression with requisite pharmaceutical effects *in vivo* in any living organism as claimed. Furthermore, the specification is silent about any positive correlation between *in vivo/in vitro* effect of an oligonucleotide consisting of SEQ ID NO:1. Moreover, the instantly claimed invention would require undue experimentation as the reference of Patil et al. teaches that a clinical application of DNA-based drugs, such as an antisense oligonucleotide of the instant application, requires careful series of trial and error tests for ensured success of bioavailability and pharmacokinetics of the DNA-based drugs due to "unpredictable pharmacokinetics" of internalized DNA-based drugs. In view of the foregoing, the instant disclosure does not provide any guidance required to overcome the art-recognized unpredictability of using DNA-based drugs in pharmaceutical applications in a mammal *in vivo*. Taken together, undue experimentation would have been needed to use the claimed invention based on the content of the disclosure (i.e., amount of direction and existence of working examples provided by the inventor) and the state of the prior art, the level of one of ordinary skill, and the level of predictability in the art. In view of all these factors and the totality of the teachings that the activity of DNA-based drugs are unpredictable *in vivo*, undue experimentation would be required of the skilled artisan to practice the instantly claimed invention, thus claim 38 is not enabled.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the RNA interference" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 42 is currently amended to recite "The agent of claim 34, wherein the oligonucleotide consists of the nucleotide sequence set forth in any one of SEQ ID NOs: 1 to 4 in the sequence listing." Applicant has elected SEQ ID NO:1 in the reply filed on July 14, 2006, which is a single-stranded 31-mer. Claim 34 recites an oligonucleotide agent that exhibits an RNA interference effect on the expression of the Asef gene. As amended, the agent claimed in claim 42 must consist of SEQ ID NO:1, which is a single-stranded 31-mer DNA oligonucleotide and no additional element. Note that the transitional phrase "consist of", unlike "comprise" or "have", excludes any element or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("consisting of" defined as "closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith."). See MPEP §2111.03. In view of the foregoing, it is internally inconsistent and ambiguous how a single-stranded DNA oligonucleotide claimed in claim 42 can inhibit gene expression by RNA interference and at the same time exhibit RNA interference effect as claimed in claims 33-34, from which claim 42 depends.

Conclusion

Claims 26, 33, 34, 38, and 42 are rejected.

An oligonucleotide consisting of SEQ ID NO:1 (34 nucleotides in length) claimed in claim 37 appears free of the prior art searched on record.

This application contains claims 27-32, 35-36, 39-41, and 44-51 as well as SEQ ID NOs: 2-4 recited in claim 42, drawn to inventions nonelected with traverse in the reply filed on July 14, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
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TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER